Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-8, 22 and 23 are pending in the application, with claim 1 being the sole independent claim. Claim 4 is sought to be amended. Support for the amendment to claim 4 can be found throughout the specification, including the claims as originally presented. No new matter is added by way of this amendment. It is respectfully requested that the amendment be entered and considered.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Claim Rejections Under 35 U.S.C. § 103

A. Effective Filing Date

The Examiner stated that:

> [T]he effective filing date for the claimed invention is August 31, 2001. Applicants' priority documents (PCT/GB00/00624, United Kingdom 9904028.9 and United Kingdom 9922561.7) have been reviewed. The claimed method was first disclosed and enabled in the pending application 09/942583, filed August 31, 2001.

See Office Action, page 3. Applicants respectfully disagree and submit that the currently claimed methods are entitled to the benefit of the filing date of the priority applications. For example, Applicants submit that the currently presented claims are supported by PCT/GB00/00624, *e.g.*, at pages 13-15, and in claim 33, which is very similar to claim 1 of the present application. Applicants also respectfully note that the Examiner has not pointed to any particular element(s) of the claims that is/are believed to be unsupported by the priority applications.

B. Van der Ley, Liljeqvist, Galen, Graham, or Blake

Claims 1-8, 22 and 24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over van der Ley *et al.*, Liljeqvist *et al.*, Galen, Graham *et al.*, or Blake *et al.* *See* Office Action, page 4. Applicants respectfully traverse this rejection.

A *prima facie* case of obviousness cannot be established unless all of the claim elements are taught or suggested by the cited references. *See In re Royka*, 490 F.2d 981, 984-85 (CCPA 1974); *see also In re Glaug*, 283 F.3d 1335, 1341-42 (Fed. Cir. 2002); *In re Rijckaert*, 9 F.3d 1531, 1533 (Fed. Cir. 1993). In addition, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998).

An element of the currently presented claims is expressing a heterologous gene product in commensal *Neisseria*. As explained below, none of the cited references teach or

suggest expression of heterologous gene products in commensal *Neisseria*. Thus, a *prima facie* case of obvious has not been established.

Van der Ley refers to a multivalent vaccine strain obtained by transforming *Neisseria meningitidis* with an additional class 1 outer membrane protein-encoding gene. (*See* Abstract and page 3156, right column, first line under "Materials and Methods"). Van der Ley does not describe or suggest expression of heterologous proteins in commensal *Neisseria*.

Liljeqvist provides a review of recombinant vaccines (*see* Abstract) and discusses a number of bacterial hosts on pages 5 - 6, section 2.4. Liljeqvist emphasizes that *E. coli* is the "dominant" bacterial expression system. Other bacterial hosts are mentioned, but these do not include any *Neisseria* species, let alone commensal *Neisseria*.

Galen relates to a "Plasmid Maintenance System" for the stabilization of expression plasmids encoding foreign antigens (*see* Abstract). However, the focus of this document is clearly on expression of antigens in *Salmonella typhi* (*see* column 6, lines 57 - 58, and column 11, lines 1 - 10). Expression in *E. coli* and *Salmonella* is also mentioned in column 25, lines 23 - 25. However, Galen does not teach or suggest expression of heterologous gene products in commensal *Neisseria*.

Similarly, Graham relates to the expression of helminth genes (Abstract). The only expression system mentioned in this document is *E. coli* (column 8, lines 1 - 2).

Blake teaches the expression of group B porins from *Neisseria meningitidis* in *E. coli* (see Abstract) and, again, does not teach the expression of heterologous gene products in commensal *Neisseria*.

In view of the foregoing, Applicants assert that there is not teaching in the cited documents relating to expression of heterologous gene products in commensal *Neisseria*. Applicants further respectfully submit that the Examiner's assertion that the claimed invention would have been obvious from the cited documents relies on hindsight. A person of ordinary skill in the art would not have had any motivation to modify established expression systems such as *E. coli* by using commensal *Neisseria*. Indeed, the large number of cited documents teaching the use of other expression systems is evidence that it would *not* have been obvious to express heterologous genes in commensal *Neisseria*.

Applicants further assert that a person of ordinary skill in the art would have had no motivation to use an alternative expression system. It is clear, for example from Liljeqvist, that some prokaryotic expression systems are more developed than others. Of these, *E. coli* is very much the dominant system, although others such as *Salmonella typhimurium* have been discussed in the art. A further discouragement from using an alternative expression system is that *E. coli* expression systems are readily available in kit form from biotechnology suppliers, whereas the use of other expression systems would be a completely new departure for the practitioner. Thus, in the absence of clear teaching to use any different expression system, the skilled person would have simply chosen one of the existing well-characterized expression systems.

Applicants would like to apprise the Examiner of a further technical consideration that renders the present invention non-obvious, namely, that the transformation of pathogenic *Neisseria* (mentioned by van der Ley) involves different technical considerations than the transformation of commensal *Neisseria* as recited in the present claims. Van der Ley (page 3157, left column, under the heading "Transformation of meningococci") indicates that *Neisseria meningitidis* were transformed by simple incubation with plasmid DNA, thus relying on the ability of meningococci to take up natural DNA. In contrast, transformation of commensal *Neisseria* was achieved by the present inventors by a different method, which is based on conjugation (*i.e.*, transfer of a plasmid into commensal *Neisseria* strains was mediated by a donor strain -- *see* Example 9 of the present application). Thus, there are particular technical considerations associated with the development of commensal *Neisseria* as an expression system that are not taught or suggested in the cited references.

In summary, the claimed invention would not have been obvious from any of the cited documents because (a) there is no teaching in the cited art relating to the expression of heterologous gene products in commensal *Neisseria*, (b) in light of the teachings in the art relating to extensively used expression systems such as *E. coli*, a person of ordinary skill would have had no reason or motivation to use commensal *Neisseria*, and (c) technical considerations would have discouraged the skilled person from using commensal *Neisseria* as an expression system. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

II. Claim Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 4 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. *See* Office Action, page 7. According to the Examiner, "[t]he claim is vague and indefinite in the recitation of 'and fragments thereof'. It is not clear if this phrase is intended to apply to all of the members of the Markush group or specifically to an outer membrane protein." *See id.*

Claim 4 has been amended to more explicitly specify that the heterologous gene product is (a) transferrin binding protein; (b) a Cu,Zn-SOD; (c) an NspA; (d) a porin; (e) an outer membrane protein; or a fragment of any of (a) - (e). In view of this amendment, Applicants believe that the rejection under 35 U.S.C. § 112, second paragraph has been fully accommodated and should be withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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